Drugs (2016) 76:315–330
DOI 10.1007/s40265-015-0519-2

THERAPY IN PRACTICE

What to Do, and What Not to Do, When Diagnosing and Treating Breakthrough Cancer Pain (BTcP): Expert Opinion

Working Group Nientemale DEI · R. Vellucci[1] · G. Fanelli[2] · R. Pannuti[3] · C. Peruselli[4] · S. Adamo[5] · G. Alongi[6] · F. Amato[7,8] · L. Consoletti[9] · L. Lamarca[10] · S. Liguori[11] · C. Lo Presti[12] · A. Maione[13] · S. Mameli[14] · F. Marinangeli[15] · S. Marulli[16] · V. Minotti[17] · D. Miotti[18] · L. Montanari[19,20] · G. Moruzzi[21] · S. Palermo[22] · M. Parolini[23] · P. Poli[24] · W. Tirelli[25,26] · A. Valle[27] · P. Romualdi[28]

Published online: 11 January 2016

Abstract Clinical management of breakthrough cancer pain (BTcP) is still not satisfactory despite the availability of effective pharmacological agents. This is in part linked to the lack of clarity regarding certain essential aspects of BTcP, including terminology, definition, epidemiology and assessment. Other barriers to effective management include a widespread prejudice among doctors and patients concerning the use of opioids, and inadequate assessment of pain severity, resulting in the prescription of ineffective drugs or doses. This review presents an overview of the appropriate and inappropriate actions to take in the diagnosis and treatment of BTcP, as determined by a panel of experts in the field. The ultimate aim is to provide a practical contribution to the unresolved issues in the management of BTcP. Five 'things to do' and five 'things not to do' in the diagnosis and treatment of BTcP are proposed, and evidence supporting said recommendations are described. It is the duty of all healthcare workers

✉ R. Vellucci
renato.vellucci@gmail.com

1 SOD Cure Palliative e Terapia del Dolore, Ospedale Universitario Careggi, Florence, Italy

2 SC Anestesia, Rianimazione e Terapia Antalgica, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

3 Fondazione ANT Italia Onlus, Andria, Italy

4 SC Cure Palliative, Ospedale di Biella, Ponderano, BI, Italy

5 UO Terapia del Dolore, ARNAS Civico di Palermo, Palermo, Italy

6 Hospice e Cure Palliative, ASP 1di Agrigento, Agrigento, Italy

7 UOC Terapia del Dolore e Cure Palliative, Azienda ospedaliera di Cosenza, Cosenza, Italy

8 Past President Feder Dolore-SICD, Cosenza, Italy

9 Struttura di Medicina del Dolore, Ospedale Universitario "Ospedali Riuniti", Foggia, Italy

10 UOS Cure Palliative e Terapia Antalgica, Azienda ULSS N. 10 "Veneto Orientale", San Donà di Piave, VE, Italy

11 USC Cure Palliative Terapia del Dolore, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy

12 UOD Terapia del Dolore e Cure Palliative, ACO San Filippo Neri, ASLRME, Rome, Italy

13 Terapia antalgica e Cure Palliative, Presidio Ospedaliero "S. Maria della Pietà", Nola, NA, Italy

14 SC Terapia del Dolore, Presidio Ospedaliero "A. Businco", Cagliari, Italy

15 Scuola di Specializzazione di Anestesia, Rianimazione e Terapia Intensiva, Università dell'Aquila, L'Aquila, Italy

16 OC Anestesia, Rianimazione e Terapia Iperbarica, UOS-I Gruppo Operatorio, Ospedale "Vito Fazzi", Lecce, Italy

17 SC Oncologia Medica, Azienda Ospedaliera "S.M. della Misericordia", Perugia, Italy

18 UO Cure Palliative e Terapia del Dolore, Fondazione Salvatore Maugeri-IRCCS, Pavia, Italy

19 UO Semplice Cure Palliative, Ravenna, Italy

20 Dipartimento Onco-ematologico, AUSL della Romagna c/o Presidio Ospedaliero Umberto I, Lugo di Ravenna, Italy

21 UOS Hospice, Azienda Sanitaria Provinciale di Siracusa, Siracuse, Italy

22 UOC Terapia Antalgica, IRCCS San Martino-IST, Genoa, Italy

23 UOC Anestesia e Rianimazione B, Azienda Universitaria integrata di Verona, Verona, Italy

24 UO Terapia del Dolore, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

involved in managing cancer patients to be mindful of the possibility of BTcP occurrence and not to underestimate its severity. It is vital that all the necessary steps are carried out to establish an accurate and timely diagnosis, principally by establishing effective communication with the patient, the main information source. It is crucial that BTcP is treated with an effective pharmacological regimen and drug(s), dose and administration route prescribed are designed to suit the particular type of pain and importantly the individual needs of the patient.

Key Points

Despite the current availability of efficacious pharmacological treatments, the clinical management of breakthrough cancer pain (BTcP) remains unsatisfactory.

A lack of consensus on essential aspects of BTcP, such as definition, epidemiology and assessment, coupled with underestimation of its severity and impact on patients' quality of life by clinicians, are key barriers to effective management of this type of pain.

Widespread prejudices concerning the use of opioid drugs frequently leads to the prescription of ineffective drugs or inadequate doses.

A practical overview of the actions to take in the diagnosis and treatment of BTcP, proposing for each of the two clinical sectors five 'things to do' and five 'things not to do', with a brief description of the evidence supporting said recommendations.

1 Introduction

Despite the large body of literature on breakthrough cancer pain (BTcP), also known as intense episodic pain (IEP) and its clinical significance in cancer-related pain, questions regarding its definition, terminology, epidemiology and assessment still remain largely unanswered. Furthermore, although efficacious pharmacological treatments for BTcP are now available, its clinical management remains unsatisfactory in many settings, indicating the need for simple and practical diagnostic and treatment protocols.

BTcP was first defined by Portenoy and Hagen in 1990 as a "transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain" in patients undergoing long-term opioid treatment for cancer-related pain [1]. This definition, and the term itself, accentuates the fact that BTcP occurs within a context of chronic pain that is otherwise satisfactorily managed, a concept that is not immediately apparent if it is referred to as IEP, or by terms such as 'episodic' or 'transient' pain, proposed in 2002 by the European Association for Palliative Care (EAPC) [2]. Portenoy's initial definition of BTcP has been refined over the years, and for the purposes of this paper we adopt that proposed by Davis et al in 2009, namely "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain" [3]. Using this definition, BTcP includes both spontaneous and incident pain. Incident pain, defined as pain occurring as a direct and immediate consequence of a movement or activity, refers to physical activities such as weight bearing in a patient with bone metastases, or dressing changes that can be predicted to worsen pain. Incident pain can include events that are volitional, such as pain with voluntary movement, or non-volitional, such as breakthrough pain caused by for example a bowel motion in a patient with bulky pelvic cancer. It is important to note that the inclusion in this definition of pain provoked, whether accidentally or not, by diagnostic and treatment procedures remains controversial. Nevertheless, using their definition as a starting point, Davis et al proposed a simple clinical algorithm for the diagnosis of BTcP (Fig. 1) [3].

The different forms of episodic pain included in the definition of BTcP reflect the different pathogenic mechanisms involved. BTcP may be somatic nociceptive (for example arising from bone metastases or contact with inflamed or infected mucosal tissue), visceral nociceptive (caused by distension or sub-occlusion of the gut, or acute episodes of tenesmus), or neuropathic (compression/distortion of a nerve or nerve root, or stimulation of a hyperaesthetic area) in origin. BTcP can be caused in various tissues or organs either by direct compression/obstruction by the tumour, as a non-specific manifestation of the latter stages of the debilitating disease [4], or as an undesirable consequence of anti-cancer treatments.

Accurate characterisation of BTcP is essential to clarify its pathogenesis, and to ensure the most suitable analgesic

[25] Centro di Terapia del Dolore, Hospice "Fondazione Roma Sanità", Rome, Italy

[26] Centro di Rianimazione e Terapia del Dolore e Cure Palliative, Istituto Nazionale Tumori "Regina Elena", Rome, Italy

[27] Fondazione FARO, Turin, Italy

[28] Dipartimento di Farmacia e Biotecnologie, Alma mater studiorum, Università di Bologna, Bologna, Italy

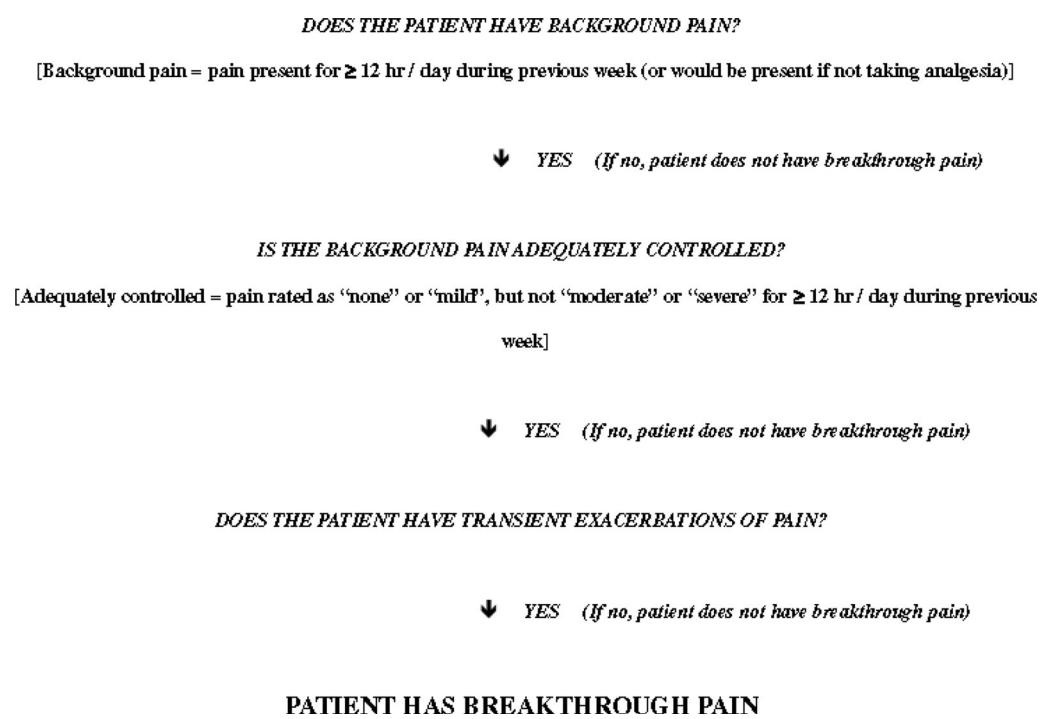

Fig. 1 Algorithm for diagnosing breakthrough cancer pain (BTcP) [3]

treatment is prescribed. Indeed, the current lack of universally accepted definition, classification and clinical-assessment tools, makes management of this type of pain problematic. Current EAPC guidelines, based on the clinical characteristics of BTcP (transient episodes of intense pain of rapid onset), suggest the use of additional doses of immediate-release (IR) oral opioids (morphine, oxycodone) or transmucosal oral or intranasal preparations of fentanyl [a rapid-onset opioid (ROO)] [5]. However, it should be remembered that IR morphine sulphate is no more effective than placebo within the first 45 minutes, and possesses pharmacokinetic characteristics unsuitable for the majority of BTcP episodes (rapid onset and short duration). Therefore it should be restricted to those cases of predictable, procedure-related pain that persist beyond 60 min [6]. ROOs, on the other hand, are faster acting and their effect is less persistent, making them the preferred choice [5, 7]. However, there are still widespread misconceptions among patients and medical personnel on the use of opioids. This, together with a tendency of the latter to underestimate the severity of the pain experienced, leads to inadequate doses or inappropriate drugs being prescribed to manage BTcP. In many cases the clinical response to such episodes is suboptimal, and more focus on the timing of administration, type and dosages of medicines used, and the individual needs of patients would improve outcomes.

With the objective of providing a practical 'what to do' and 'what not to do' guide for healthcare professionals involved in BTcP management, a panel of experts from Italy reviewed and assessed the clinical and pharmacological aspects of BTcP from first principles. This was a multidisciplinary group of oncologists, pain and palliative care physicians who were all members of SIAARTI (Italian society of Anaesthesia, Analgesia, Reanimation and Intensive Care Specialists) with the ultimate aim of improving the lives of their patients. This is not intended as a consensus report with validated recommendations and levels of evidence but rather an initial contribution in tackling one of the most important issues today in oncology and palliative care that in Italy, to date, no scientific society has addressed.

2 Diagnosing BTcP: Five Things to Do

2.1 Assess for Both 'Idiopathic' and 'Incident' BTcP at All Stages of the Disease

The reported prevalence of BTcP in patients suffering from cancer-related pain varies widely, with figures ranging between 40 and 80 %. A survey conducted by the International Association for the Study of Pain (IASP) reported BTcP in 64.8 % of 1095 patients with cancer-related pain, particularly those with more severe background pain and functional impairment [8]. However, none of the numerous studies on the prevalence of BTcP has found any

statistically significant link between BTcP and either the intensity of background pain or the extent of the disease [9]. Very little data are available on the Italian situation, but percentages of between 40 and 50 % have been reported [10–12]. BTcP may occur at any stage of cancer [9], and although there is no consensus regarding its prevalence, it is clear that it does occur in a significant number of patients with cancer-related pain, having a significant impact on quality of life. It is therefore essential that all the various manifestations of BTcP (spontaneous and incident) are included in diagnostic assessment and monitoring of all cancer patients, particularly in those with advanced disease. In fact, according to the American Pain Foundation, BTcP occurs in up to 89 % of later-stage cancer patients, but also in 35 % of oncology outpatients [13]. Although BTcP is more common in late- and end-stage cancer patients, its impact is greater in the early stages, so these patients need to be assessed accurately.

2.2 Carefully Assess BTcP Features (Triggers, Intensity, Duration and Frequency of Episodes) and Attendant Psychological and Social Factors

As a specific nosological entity, BTcP presents with distinctive features, specifically an episode of intense pain, typically of rapid onset (within a few minutes), limited duration (a mean of 30 min), and a frequency that ranges from between one and four times a day, but clinical presentation may vary considerably from patient to patient. For example, in most patients the pain peak is reached within a very short time, whereas in episodes caused by visceral distension its onset may take several minutes. Moreover, almost one third of BTcP patients report more than four episodes a day [1, 4]. Accurate diagnosis therefore requires careful assessment of the specific characteristics of an individual patient's pain, including time of onset, duration, peak intensity, relationship to background pain, location, type, and particular features, as well as any triggers and effects on their daily routine and/or quality of life. It is particularly important to focus on the relationship between BTcP and background pain, which can fluctuate over time, and at its peak may be confused with BTcP. This will have obvious consequences on pain management, so particular care must be taken to differentiate between the two. International pain scales may be helpful [3], considering that the intensity of BTcP is greater than the daily mean background pain [at least 3 points on the numeric rating scale (NRS) pain scale].

As there are no specific tools for diagnosing BTcP, careful clinical assessment, based on thorough case history and objective testing is vital. Clearly the patient's input is essential, and the physician will need to enlist his/her help by providing up-to-date and exhaustive information on this type of pain, investigating its occurrence and features. The importance of psychosocial factors is also recognised by today's cancer-related-pain classification systems, and these need to be carefully assessed. Factors to be investigated include previous experience of pain, social status, cognitive factors and psychological stressors. Psychological stress has been closely linked with the intensity of cancer-related pain, and should be included in pain assessment [14]. Cognitive skill is also an influential variable, and can considerably affect both the perception of pain and the ability to describe it. Psychosocial or emotive stimuli can act as triggers for incident pain to a similar extent to physical stimuli [15]. It is important therefore that the impact of such stimuli is taken into account in assessment and pain management strategies (prescribing the appropriate psychological and/or pharmacological therapies). Most importantly, the perceived intensity of the pain should never be underestimated, and clinical assessment of BTcP needs to be exhaustive, comprising evaluation of both physical and psychosocial variables, in order to get a complete picture of the individual case.

2.3 Consider Differential Diagnosis Between BTcP and End-of-Dose Pain

As the analgesic effect of baseline pain medicine wears off, episodes of pain are not infrequent in cancer patients. They can occur, for instance, with opioids administered twice daily, and with some transdermal systems that do not always guarantee 72-h coverage. These episodes are linked to the background pain, and do not arise from the specific pathological mechanisms of BTcP. Indeed, in such cases the prerequisite for diagnosis of BTcP, namely well-controlled background pain, is lacking. From a pain management standpoint, end-of-dose pain should be considered as background pain, despite that fact that some authors suggest that it is a subtype of BTcP [3, 15–19].

Differential diagnosis of the two types of pain can be based on the clinical features of end-of-dose pain, whose onset, which is generally slower and progressive, coincides with the period antecedent to the next dose. The frequency of such episodes also provides a clue, being linked to the frequency of analgesic administration. In summary, the characteristics of the pain onset, frequency, time frame and duration need to be considered to ensure accurate differential diagnosis between the two types of pain.

2.4 Use Assessment Tools to Support BTcP Diagnosis

Although effective management of BTcP depends on careful assessment of its features, no single effective tool for its accurate diagnosis is a yet available. Furthermore, it

generally presents features that are not measured by existing tools for assessing cancer-related pain (temporal features and triggers). Several authors have recently proposed algorithms for use in BTcP diagnosis [3, 12], and while these do have some clinical utility in identifying patients, further tools are needed for its characterisation and management. Existing algorithms are plagued by questions such as what precisely is "well-controlled background pain", a somewhat vague definition that it is difficult to determine in clinical practice. The various tools proposed for assessing BTcP include the Breakthrough Pain Questionnaire (BPQ) drawn up by Portenoy and Hagen [1], which has been used in various clinical trials but has not yet been formally validated, and the Alberta Breakthrough Pain Assessment Tool (ABPAT), which has been validated in collaboration with patients and experts in the field but is rather too complex for routine clinical practice [20]. A re-worked, simplified version of the ABPAT has recently been proposed by Mercadante et al (Fig. 2) [11].

The Breakthrough Pain Assessment Tool (BAT) was developed to simplify BTcP assessment. This comprises 14 questions regarding the temporal, qualitative and therapeutic features of BTcP (Fig. 3), which are intended to facilitate diagnosis, management and periodic monitoring of BTcP patients in a variety of clinical settings [21]. Apart from their specific differences, all the BTcP assessment tools developed to date aim to act as a guide for the clinician, helping to investigate the characteristics of the individual patient, who remains the best source of data. In this context, patients should be advised to keep a 'pain diary' to monitor the fluctuations and features of their pain on a daily basis (Fig. 4). The advantage of the patient keeping a record of their symptoms in real time is that it is more reliable than retrospective memory, although it will undoubtedly take up more of the

1. *How intense has the background pain been recently (from 24 hours to several days), on average?*
2. *What medicines are being taken regularly to control background pain?*
3. *At which doses and for how long?*
4. *Is the treatment being given sufficient to control background pain for the greater part of the day?*
5. *Have sudden increases in pain been experienced?*
6. *What is the average intensity of these episodes?*
7. *How many episodes have been experienced per day/per week?*
8. *How fast do they develop?*
9. *How long do they last?*
10. *How intense do they get?*
11. *Are they the same as or different to background pain?*
12. *Do they arise spontaneously or are they triggered by a particular activity?*
13. *Do they regularly occur before administration of the scheduled analgesic?*
14. *What impact do they have on daily routine?*
15. *Are any activities avoided as a result?*
16. *What lessens the pain?*
17. *What specific treatment has been prescribed and for how long?*
18. *Which medicines have been prescribed and at what doses?*
19. *Are they efficacious?*

Fig. 2 Patient questionnaire for use when assessing breakthrough cancer pain (BTcP) [11]

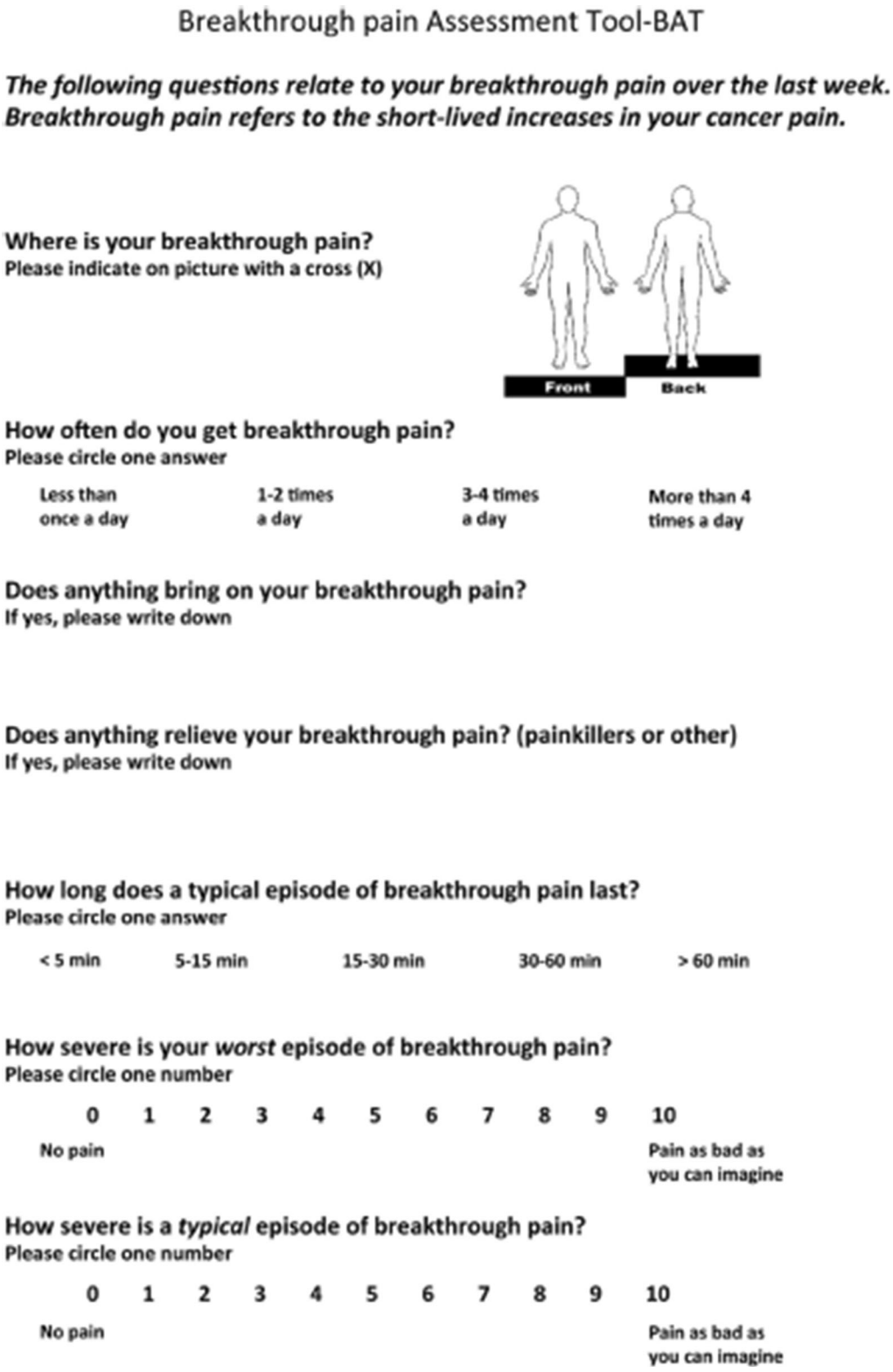

Fig. 3 Breakthrough pain assessment tool (BAT) [21]

clinician's time to interpret the information recorded. The important thing to remember when proposing such a strategy is to keep the process as simple as possible in order to maximise compliance (patients are unlikely to adhere to time-consuming complex monitoring schemes) [22].

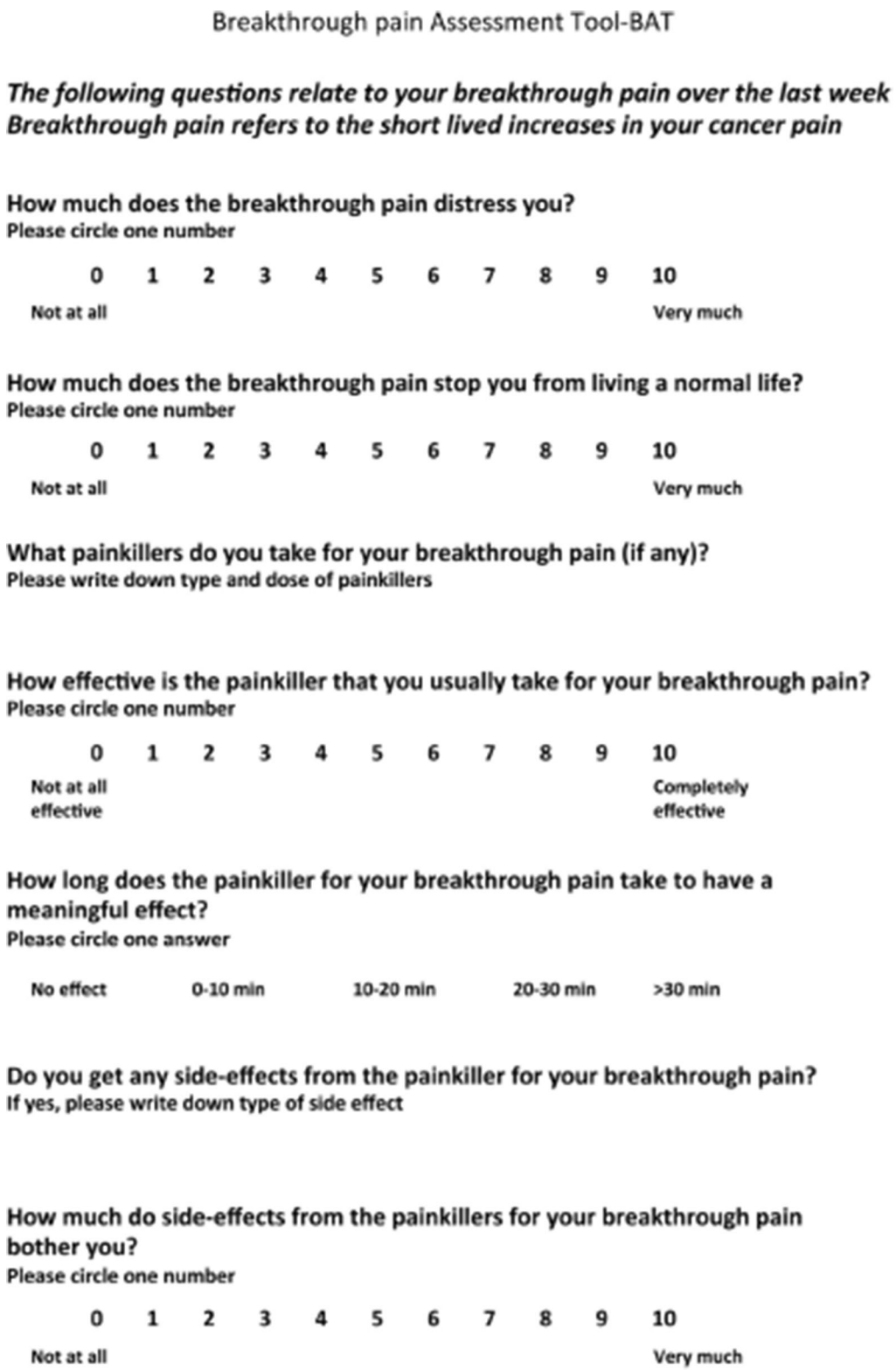

Fig. 3 continued

In conclusion, specific tools for assessing and monitoring BTcP do exist, and should therefore be used by the medical caregiver to help build a comprehensive picture of their patient's clinical situation. It is hoped that in future these will be further validated and refined, in particular so that they can be applied to non-English-speaking patients.

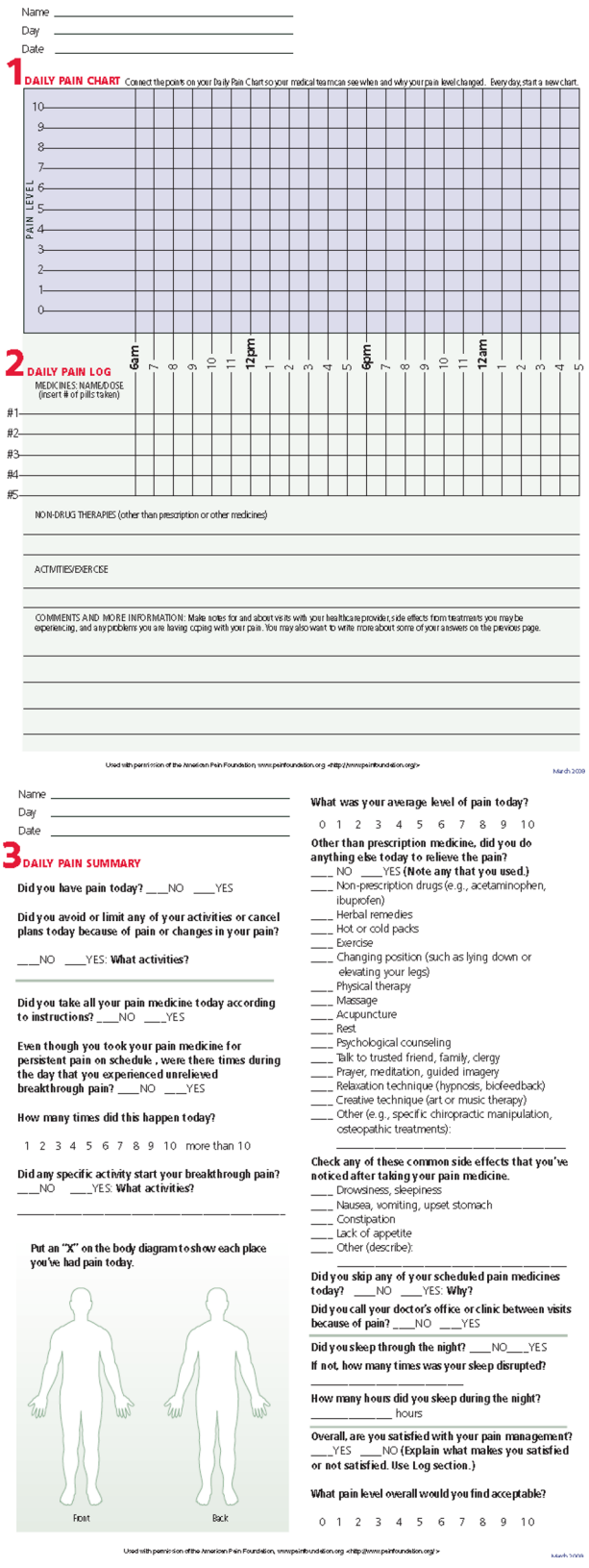

Fig. 4 Pain diary, as developed by the American Pain Foundation

2.5 Assess the Patient's Adherence to Their Treatment for Background Pain

As BTcP, by definition, occurs against a background of well-controlled pain, optimisation of baseline analgesic treatment is essential for an accurate diagnosis. Patient compliance to prescribed analgesic treatment needs to be ascertained and monitored by various means (patient self-assessment, pill counts, laboratory testing), some more effective than others. Compliance is notoriously the bane of prescribing physicians, but takes on particular significance in BTcP, which cannot be reliably diagnosed without it. A range of adherence levels has been reported in cancer patients given opioids for pain management, varying from 50 to 90 % [23], illustrating even in the best-case scenario, a significant number of patients do not adhere to baseline treatment. The main barriers to compliance may be cognitive (resistance to opioid use) and/or symptomatic (previous or current experience of unwanted side effects), but this can be contrasted to some extent by open and informed communication between patient and physician [24, 25]. As yet there are no specific adherence monitoring tools for cancer patients, still less for BTcP, and it is hoped they will be forthcoming, despite the inherent difficulties in designing them [23]. Meanwhile, one way of carrying out the vital task of monitoring adherence to analgesics (and any missed doses) is to use a 'pain diary', which should therefore include specific questions to that effect.

3 Diagnosing BTcP: Five Things Not to Do

3.1 Underestimate the Complexity of Diagnosing and Managing BTcP

As there is no single consolidated definition of BTcP, whose pathogenetic mechanisms have only in part been determined, and no specific assessment protocol has been accepted, this type of pain is particularly difficult for the clinician to diagnose and treat. This complexity, and the attendant resources required, should not be underestimated by caregivers. In addition to the above-mentioned nosological issues, when diagnosing BTcP it is essential to consider the impact of this type of pain on the patient's quality of life (QoL). Indeed, aside from the intense pain, it may cause sleep disturbances, psycho-emotive deficits, and affect interpersonal relationships, limiting a person's ability to work (especially in jobs requiring concentration and attention) and/or go about their daily life. According to a survey carried out by the American Pain Foundation in 2010, 85 % of the patients interviewed reported that BTcP

had a negative impact on their QoL, and 91 % felt that this could be significantly improved by better management [26]. In BTcP management, the tendency to underestimate the impact of BTcP is evidenced by the substandard treatment often given to such patients. This may be a consequence of various cultural, educational, political, religious and logistic factors, as well as those relating to healthcare resource management [13]. In the latter, it is essential to weigh the absolute cost of the drugs used to treat BTcP against those arising from poor management, which will entail more frequent and longer periods of hospitalisation and consultation, as well as indirect costs for the healthcare providers and patients [27, 28].

Poor management of cancer-related pain is particularly common in the elderly, as revealed by the SAGE (Systematic Assessment of Geriatric Drug Use via Epidemiology) Study Group, who reported, 26 % of elderly patients experiencing pain do not receive any analgesic treatment, 16 % receive only drugs ranked at the bottom of the WHO pain ladder, 32 % those on the middle rung, and only 26 % are given morphine or other powerful opioids [29]. It is evident therefore that BTcP cannot be managed successfully without recognising both its importance and complexity.

3.2 Fail to Spend Sufficient Time Recording Patient History and Carrying Out Objective Tests

Generally speaking, a satisfactory doctor-patient relationship cannot be established and maintained without the former taking the time to involve the latter in compiling accurate medical records, complete with all the necessary objective tests. This is particularly important in BTcP, as no specific diagnostic tools or tests are yet available, meaning that diagnosis is entirely based on the information collected from the patient by the physician [30]. When recording the features of a particular case, it is crucial that the patient is questioned in a suitable manner, using language that they will find easy to understand, and that objective diagnostic tools are used whenever possible. In order for this to be carried out effectively, it is vital that sufficient time is set aside. Indeed, objective examination is not only aimed at assessing the general conditions of the BTcP patient, but also at discovering any underlying causes that may be resolvable, for instance allergic-rhinitis-related cough or vertebral fractures. Hence, in some cases, in addition to clinical examination, it may be useful to perform CT or MRI to get a detailed picture of the soft tissues or nervous system, despite the inability of such techniques to diagnose BTcP itself, which, as mentioned, must be diagnosed clinically [22]. It is clear, therefore, that good management of BTcP is reliant on accurate assessment of the patient [3], which in turn depends on the time dedicated to achieving this end.

3.3 Disregard Patient Information About Their BTcP

The patient is the most reliable source of information on the nature and intensity of their BTcP. Nevertheless, the nature of pain symptoms may lead to the doctor to disregard or underestimate the patient's statements and self-assessment regarding the intensity of their pain [31, 32]. Such a tendency may be influenced by factors relating to the patient, physician and their respective cultural contexts. For instance, elderly patients are often considered to be less reliable reporters, as are those who use emotive language to describe their pain. Generally speaking, people from disadvantaged socio-cultural backgrounds are less able to describe their symptoms with a great degree of precision, and this may lead the physician to take a more sceptical view of the patient's account. It is therefore important to take a patient's socio-economic characteristics into consideration, alongside their cultural and psychological make-up, when conducting a thorough assessment of the pain experienced.

3.4 Underestimate the Negative Impact of BTcP on Cancer Patient Management

We have seen that BTcP includes both spontaneous and incident pain and in one study in 63 patients with BTcP, 55 % were found to have incident pain, the majority provoked by some kind of movement on the part of the patient (volitional pain) [1]. Similarly, the 12-month IOPS (Italian Oncologic Pain Survey) in around 1500 cancer patients found that 44 % of BTcP could be classified as incident-type, as compared with 56 % classed as spontaneous. In practical terms, therefore, roughly half of BTcP episodes are provoked by some kind of stimulus. As this will have major repercussions on the treatment prescribed, not to mention the impact on the patient, differential diagnosis of the type of BTcP experienced is essential. According to a classification system proposed by Parlow et al, incident-type pain (in end-stage cancer patients) can be divided into three categories: precipitated by bedside care (turning, bathing, changing the bed linen), mobilisation (getting up, going to the bathroom), and by therapeutic procedures (changing wound dressings, physiotherapy) [33]. In the latter category, radiotherapy-associated pain, due to prolonged immobilisation or devices used to achieve it (masks, etc.), or to complications of the treatment itself (tissue irritation, mucositis, proctitis) has particular clinical implications [34]. Thus, the impact of incident pain on management of BTcP, and potential causes needs to be thoroughly investigated in all cancer patients in order for appropriate action to be taken.

3.5 Use Obscure Language When Communicating with the Patients and Their Relatives

Terms like 'BTcP' and 'intense episodic pain' mean very little to the uninstructed patient, and therefore appropriate language must be used when talking with patients, starting, for example, by asking them to describe a recent episode of intense pain they have experienced [22]. Effective communication with patients and their caregivers is always a challenge, but it is particularly important in BTcP, whose diagnosis is based almost exclusively on anamnesis. Self awareness is key when dealing with a patient, as is remembering that some things that may be taken for granted by medical personnel will not necessarily be apparent to the patient. Studies conducted in cancer patients show that it is difficult for them to distinguish the difference between background pain and BTcP, but that a clear, comprehensive explanation provided by the physician on the features and causes of their pain can significantly help to alleviate their suffering [35]. Good communication skills can also aid the physician in determining the most efficacious management strategy and ultimately improve compliance and significantly influence the patient's attitude to analgesics in general and opioids in particular [36].

4 Treating BTcP: Five Things to Do

4.1 Prescribe Rescue Medication When BTcP Not Adequately Controlled

There is good evidence in the literature that BTcP is an indicator of worse clinical outcome and of lower efficacy of using opioids, exposing the physician to the problems of a therapeutic failure. BTcP can decrease functional capacity and increase levels of depression and anxiety. BTcP also represents a social cost in terms of productivity, and weighs significantly on the patient and the caregiver. As most BTcP episodes peak in intensity within a few minutes and last for 30–60 min, the speed of analgesic onset is crucial for an effective pain-management strategy. Oral opioid immediate release (IR) preparations such as morphine or oxycodone may however, not be suitable for treating many episodes of BTcP and recent data show that the ROOs provide superior pain relief within in the first 30 min after dosing [37] (Table 1).

Although moderate-to-severe cancer-related pain has long been treated using (generally orally) morphine, 2012 EACP guidelines recommend the use of other powerful opioids, namely oxycodone or hydromorphone, with no distinction between the two, as the first-line option in such cases [5]. In order to be able to compare and cycle between these different opioid treatments, their dosage can be expressed as 'equivalent' to the morphine standard, and calculated using the appropriate conversion charts.

Table 1 Characteristics of opioids used for BTP (times in minutes)

	Analgesic onset	Availability	Dwell time
Oral morphine	30–45′	30	NA
Oral oxycodone	30–45′	40–50	NA
OTFC	15–30	50	15
FBT	15	65	15
SLF	10–15	70	2
FBSF	15	65	2–5
INFS	5–10	80–90	NA
FPNS	5–10	70	NA

BTP breakthrough pain, *FBT* fentanyl buccal tablet, *FBSF* fentanyl buccal soluble film, *FBNS* fentanyl pectyn nasal spray, *INFS* intranasal fentanyl spray, *OTFC* oral transmucosal fentanyl cytrate, *SLF* sublingual fentanyl

In a population of patients whose background pain is well-controlled using systemic opioids, it is difficult to establish the actual percentage affected by BTcP, but as mentioned above, it appears to be around half. It is therefore particularly important in such cases to consider the possibility of BTcP onset, and to provide for a rescue dose alongside the regular analgesic treatment regimen to treat any episode of intense pain that breaks through. Although this concept is well established, the study by Zeppetella et al of hospice patients with cancer showed that 43 % of those being treated with 'strong' long-acting opioids to control their background pain were not prescribed rescue medicine, despite episodes of BTcP [4]. In an Italian study, rescue medicine was not provided in a reported 34 % of cases [10]; however, both these studies were carried out a number of years ago and these figures may now have improved. Indeed, it is hoped that by now clinicians are more aware of the issue, providing their patients with up-to-date information regarding the features of BTcP, the possibility of its onset, and the choices for rescue medication. The purpose of rescue medicine is to treat BTcP as distinct from background pain. This means that it is relatively independent of the treatment for the latter, and will be chosen on the basis of the features it presents. The features that distinguish BTcP from fluctuations in background pain include a discernible trigger, rapid onset, high intensity and relatively repetitive episodes. Patients with painful episodes with these symptoms should be given specific treatment for BTcP. Providing the patient with rescue medication in advance has a significant impact on both the patient's wellbeing and the burden on the healthcare provider. At this difficult and emotional time it is reassuring for patients and caregivers to know there is a plan of action to deal with acute episodes of pain. From a healthcare-provider standpoint, the availability of an

effective treatment for controlling episodes of BTcP helps to reduce the burden on the emergency services (as this type of patient will be less likely to present at the Accident and Emergency Unit) as well as that associated with hospital admissions and outpatient treatment [27].

4.2 Provide Suitable Treatment (Rapid-Onset Opioids, ROO) in BTcP, Whether Incident or Idiopathic

As BTcP episodes are transitory and of rapid onset [4], it is essential to use rapid-onset analgesics of relatively limited duration, high efficacy, low toxicity and relative ease of use in such cases. BTcP was originally treated with IR oral morphine, but because its analgesic action takes roughly 30–40 min (Table 1), its use has been superseded by ROOs. These powerful opioids, including fentanyl, due to their fast action, brief duration and ease of administration via the transmucosal route (oral or nasal), have now become the treatment of choice [37]. As well as being easy to access, the transmucosal route is appreciated by patients, and permits the onset of analgesia within 6 min [38–40]. Fentanyl in particular is a powerful opioid (80–100 times more powerful than morphine) that acts as a pure selective μ-receptor agonist; it is highly lipophilic, and shares the safety profile typical of opioids. The efficacy of oral and intranasal transmucosal fentanyl in managing BTcP has been confirmed in several randomised trials [41–44], which have demonstrated the superior efficacy of such preparations in controlling pain with respect to both a placebo and morphine. These studies have also demonstrated that the intranasal route provides more rapid analgesic action than oral transmucosal administration [5, 45].

These observations are the basis of current evidence-based EACP guidelines for the treatment of cancer-related pain, which state that, although oral IR opioids are viable options, oral or intranasal fentanyl (ROO) is the treatment of choice in cases of BTcP, thanks to its more rapid action and shorter duration [5]. However, the EACP only provide summary recommendations for the treatment of predictable BTcP. In such cases the guidelines suggest the preventative use of IR opioids with short half-life in the 20–30 min preceding the known BTcP trigger [5]. Importantly, patients need to be opioid naïve (either never had an opioid or have not received repeated opioid dosing for a 2- to 3-week period) to receive rapid-acting fentanyl products.

4.3 Titrate the Rescue Dose for Each Patient, Identifying the Minimum Efficacious Dose

According to the technical specifications, of all the ROOs on the market, the rescue medicine dosage should be titrated for suitable analgesia and to minimise the risk of adverse effects. The suggested titration techniques are slightly different for each drug, but a simple titration scheme, such as that suggested by Davies et al., can be used, reducing or increasing the initial opioid dose according to its efficacy (whether or not it controls the pain) and toxicity (appearance of side effects) (Fig. 5) [3]. Care should be taken in strictly adhering to licenced dosages, in a single day, patients should not be treated with rapid-acting fentanyl more frequently than every 4 h and no more than 6 doses/day. Individuals who require more frequent administration may develop toxicities. Clearly, such schemes can only be effectively employed if the right rescue medication, sure to control the pain within the timeframe of the episode, is in use, otherwise there is a risk of unwarranted dosage increases to compensate for the failure of drugs with a more delayed action.

The heterogeneity of BTcP triggers, pathogenetic mechanisms, clinical presentation and severity of episodes make it unlikely that a standard rescue medicine formula applicable to all cases will be defined. The simplest solution to this problem, calculating the rescue dose as a percentage of daily doses of background opioids, was formulated before the advent of transmucosal fentanyl, when oral morphine was generally considered the treatment of choice for BTcP episodes. Moreover, the existence

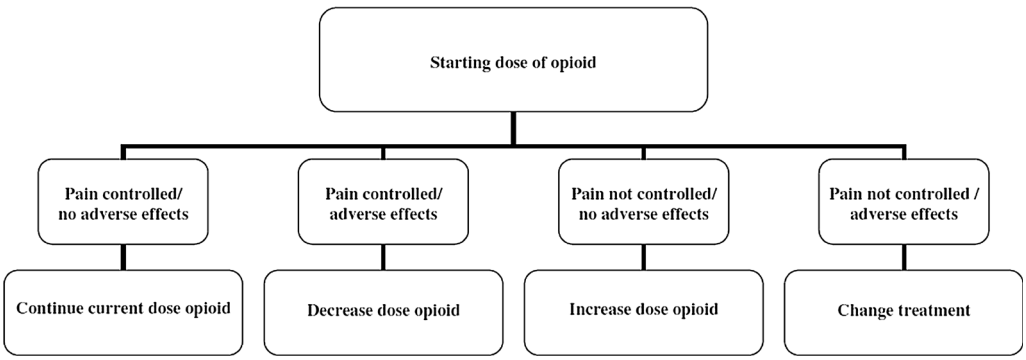

Fig. 5 Rescue drug titration scheme

of any correlation between daily dose and rescue dose sufficient to warrant the use of this formula is hotly disputed in the literature [46–48]. Retrospective studies, conducted after the optimal rescue dose had been determined by titration, do however suggest the use of a mean of 15 % of the daily dose [49–51].

Nevertheless, in the absence of robust evidence-based guidelines, titration appears to be the best solution available, particularly in more fragile patients or those on low-dose opioids for background pain. That being said, titration is labour-intensive and fraught with practical issues, requiring the prescribing physician to possess a certain degree of skill and knowledge of the pharmacokinetic profiles of the drugs used, [52] not to mention the good will (compliance) of the patient.

Given the extreme variability of BTcP episodes in the same patient, ideally each dose of ROOs would be titrated, but this is not always practicable, particularly in home-care or end-stage patients. Furthermore, issues related to specific (in patients treated with the same opioid) and cross-tolerance (in patients treated with a different opioid) can also arise, a factor that also needs to be considered when determining the optimal dose. Indeed, it will affect the determination of the rescue dose in both titration and proportional (percentage of daily dose) strategies, especially if the patient is already on high-dose opioids. All these issues will have an impact on clinical practice, and therefore titration of ROO doses for BTcP control is often performed starting with doses higher than the minimal dose that is theoretically available, or neglected altogether [52]. Some of these issues can be overcome thanks to the availability of analgesics that offer great flexibility in terms of posology, and thereby enable optimal personalisation of treatment. This will to some extent reduce the number of dropouts due to inappropriate individual doses during the titration phase.

4.4 Tailor the Route of Administration to the Individual and Provide Comprehensive Information on the Pros and Cons of Available Options

It is vital that the patient and their caregivers are fully informed as to the advantages and disadvantages of the treatment options available (possible side effects, etc.), so that they can be actively involved in the decision-making process. This is by no mean easy, as even among the ROOs (the recommended treatment for BTcP) there are many different formulations and delivery systems available—ROOs can be administered via the oral transmucosal route, using sublingual tablets, orodispersible tablets, dissolving films, tablet applicators, etc., or the intranasal route, using various types of nasal spray [39, 53]. Choosing the most suitable formulation must take into account its bioavailability and rapidity of action (nasal sprays are more rapidly absorbed), as well as its ease of use and any concomitant health issues (rhinopharyngitis or oral mucositis). It is essential to involve the patient and their caregivers in this decision to ensure the maximum adherence and therefore efficacy. Moreover, in the absence of guidelines recommending one formulation of fentanyl over another, the physician has a duty to outline to the patient the respective merits (and drawbacks) of the various options, and to take their wishes into account. The patient and caregivers need to be informed of any possible side effects of their BTcP medicine, for example with ROOs, nausea, vomiting, drowsiness and dizziness, and the fact that these will tend to diminish the longer the drug is taken [53]. A fully informed patient is more likely to be compliant and to refer any side effects they experience, making it easier to implement strategies to mitigate such effects.

4.5 Regularly Reassess On-Going Treatment and Determine the Cause of Non-Adherence

Establishing an appropriate individual treatment regimen with the BTcP patient is only the beginning. Indeed, it is essential that the patient and their treatment are regularly reassessed, using the tools outlined above (particularly after changes in the latter) so that any ineffective or inappropriate strategy can be adjusted or interrupted altogether [3]. Reassessment should not be limited merely to the efficacy of the on-going treatment (reduction of pain intensity and to what degree, duration of analgesia), but must also take into account equally important features such as daily routine and quality of life (if and to what extent the patient is able to carry out their daily activities, to what extent this is affected by pain, how they would score their overall well-being), as well as the appearance of any side effects (to be thoroughly explored through specific questioning) [22]. It is also helpful to periodically assess the patient's satisfaction (and that of their caregivers) in the care that is being given, and any difficulties they might be experiencing in their treatment. The BTcP assessment tools, as well as generic pain scales, will be useful in this regard, but once again a pain diary represents a richer source of information.

Follow-up assessment should not only be aimed at adjusting treatment if necessary, but also at assessing and promoting compliance. Indeed, while there are many reasons for poor adherence (lack of conviction of treatment efficacy, resistance to opioids, appearance or fear of side effects) all of them can be overcome to some extent by effective communication between the doctor and patient [23]. Via careful periodic assessment of patient compliance, the physician should be able to identify any barriers and take the appropriate action to remedy the situation, e.g.

adjusting the dose of any drug perceived as inefficacious, treating side effects where possible or explaining their transitory nature, and/or providing objective information on the properties and safety profile of a particular medicine.

5 Treating BTcP: Five Things Not to Do

5.1 Delay Starting Treatment

BTcP has a significant impact on the well-being and treatment course of the cancer patient, and should therefore always be dealt with appropriately. It is essential that such treatment is planned for and administered as soon as possible, so that the patient is not left exposed to this type of pain. This is more difficult than it sounds, and there may be many factors conspiring to delay the commencement of appropriate treatment. First and foremost, as BTcP by definition occurs against a background of cancer-related pain, it may be that BTcP is not even considered, much less detected, until the background medicine has been adequately titrated and the dosage regimen established. Nevertheless, it is important to watch out for the typical signs of BTcP even at this early stage, in order to distinguish it from fluctuations in background pain or end-of-dose pain. For early diagnosis and suitable intervention, detailed investigations to detect the specific features of BTcP should be carried out from the very start of analgesic treatment.

Delays in treating BTcP may also arise due to poor doctor-patient communication. If a patient is not suitably informed as to its features and the various treatment options, they may think that pain spikes are inevitable or linked to difficulties in adjusting to their daily treatment regimen, and therefore may neglect to tell their physician of any BTcP episodes they experience for some time. Clearly then, if BTcP is to be diagnosed and treated without delay, thereby ensuring the maximum benefit to patients, it is essential to establish and maintain effective communication.

5.2 Prescribe Analgesic Treatment on a Fixed Schedule Without Providing for an 'as Needed' Treatment for BTcP Management in Each Case

As BTcP episodes generally occur from 1 to 4 times a day on average [3], they may, in some cases, be predicted to a certain extent. This is particularly true if BTcP is brought on by triggers that occur at certain times and with a certain frequency, for example eating, washing, or changing the bedclothes [34]. According to the Association for Palliative Medicine of Great Britain and Ireland, however, rescue medication for BTcP should be taken as needed, and not at any specific time. They recommend administration as soon as the pain symptoms arise in the case of spontaneous or non-volitional BTcP, and prior to any precipitating event to prevent incident episodes [3]. As mentioned above, the concept of rescue medicine differs considerably from normal analgesic treatment, both in terms of its pharmacology and pharmacokinetics, and represents an essential component of treatment for cancer-related pain. As such it cannot be omitted from the treatment plan, and specific drugs for BTcP (ROO) must always be prescribed, adjusting the administration schedule according to the specific needs of the patient and the specific characteristics of their BTcP.

5.3 Use Drugs Inappropriately in Terms of Their Type (e.g. NSAIDS, Paracetamol), Dosage and/or Administration Routes

The suitability of a treatment for BTcP needs to be determined on the basis of the type, dose and administration route that best suits a particular patient. As regards the type of drug, at present, ROOs are the best available option for BTcP, and should therefore be considered the first-line treatment [5, 46]. Nevertheless, other drugs are often used as a first resort for BTcP treatment in routine clinical practice, namely oral IR morphine, paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs). Considerations as to the analgesic efficacy of such medicines aside, none seem to possess the pharmacokinetic properties required for treating BTcP (the onset of analgesic action of oral paracetamol and NSAIDs is 15–30 min, reaching its peak efficacy at 30–90 min) [3]. According to the Italian Observatory of Palliative Care, 76.5 % of physicians routinely prescribe other rescue medications as alternatives to fentanyl in BTcP. The most commonly used drugs are oral IR morphine in 51.4 % of cases, parenteral IR morphine in 29.4 % of cases, and NSAIDs in 11.4 %. IR morphine is often preferred in BTcP caused by predictable triggers, and parenteral administration of IR morphine, whose efficacy seems comparable to that of transmucosal ROOs [45], may be justified in certain clinical conditions (patients already on continuous morphine infusion, difficulties in oral administration), while NSAIDs are used by some clinicians to treat particular forms of episodic pain, such as that triggered by bone metastases [54]. However, particular clinical situations apart, and despite the need to tailor BTcP treatment to the particular characteristics of a patient, generally speaking the use of drugs other than ROOs in BTcP management should be discouraged.

Inappropriate choices may also be made in terms of administration route. Many drugs are administered by the oral route and, as we have seen, their absorption times and onset of action are not compatible with the features of BTcP (rapid onset, short duration). Intramuscular injection

also suffers from the same issues, while intravenous and subcutaneous administration offer rapid action, they are limited by practical and organisational concerns. Hence the transmucosal route—oral or nasal—should be the route of choice for BTcP, thanks to rapid the absorption it allows [38, 39].

Likewise, as with all medicines, it is important to get the dose of ROOs for BTcP right. There are many factors underlying mistakes in this regard, particularly setting the dose too low. These factors are both physician- and patient-related, and will be discussed below. But suffice it to say, for the time being inefficacious treatment due to under-prescription should be avoided at all costs.

5.4 Enhance treatment for Background Pain

By definition, BTcP occurs against a background of well-controlled pain. The first step in diagnosing such episodes is therefore to ensure that the patient's usual analgesic regimen is efficacious, and EACP guidelines state that suitable titration of baseline opioids must always precede administration of rescue medication for BTcP [5]. If background pain is not successfully managed by the existing regimen, it will require suitable adjustment via, for example, increasing the daily dose, adding adjuvant drugs, or switching opioids (bearing in mind that invasive treatments such as intraspinal administration are also options if other routes are inefficacious [3]).

That being said, there are no grounds for treating properly diagnosed BTcP by enhancing the existing treatment regimen. The features that set BTcP apart from spikes in well-managed background pain are not linked to opioid inefficacy, but to particular pathogenetic mechanisms. BTcP therefore necessitates a specific, distinct treatment rather than an increase in the daily dose, which will only result in an increase in the likelihood or severity of adverse collateral effects.

5.5 Use Suboptimal Doses of Opioids Due to Concerns About Their Safety

Concerns about the possible adverse events of opioids remain one of the principal barriers to efficacious treatment of cancer-related pain in general, and BTcP in particular [55]. This concern is often shared by both the physician and patient, particularly if the latter is inadequately informed about the safety profiles of prescribed drugs [56]. This may ultimately result in a lower than optimal dose of ROOs being prescribed and/or taken for BTcP, with consequent implications on efficacy. It is worth mentioning, therefore, that clinical trials on these drugs in the management of BTcP have demonstrated their safety. All formulations of ROO appear to be well tolerated, with only minimal local toxicity and similar safety profiles to other opioids [44, 57, 58]. Adverse events are mainly limited to nausea and vomiting, and, while it is true that they are more likely in acute administration and in concomitant administration of baseline opioids, their incidence tends to diminish over time. Furthermore, their overall prevalence in cases treated with ROOs is only roughly 5–10 %. Similarly, the other possible adverse events, including dizziness, drowsiness and headache, are generally mild–to-moderate in degree, and experienced by less than 5 % of patients.

Thanks to their perception as short-acting drugs with few adverse effects, not to mention their efficacy, ease of administration and rapidity of action, transmucosal ROOs are one of the most willingly accepted opioids. In order to further promote patient acceptance, the dose of ROOs must be carefully calibrated and adjusted to suit the individual needs of each patient with BTcP, taking into account the findings of clinical assessment of their efficacy and tolerability, and avoiding suboptimal doses. Indeed, under-prescription brings no appreciable benefit to the patient, only adding to their pharmacological load, and potentially compromising compliance.

6 Conclusions

Many critical issues still plague the diagnosis and treatment of BTcP. From a clinical perspective all members of the healthcare team assisting the cancer patient need to be aware of the possibility of BTcP occurring and not underestimate its severity and to implement timely procedures and protocols for its early and accurate diagnosis. The first step in such protocols must be careful assessment of the clinical issues affecting a given patient, who is the principal source of valuable diagnostic information and must therefore be kept fully informed using appropriate language. The second step is to administer effective treatment at the appropriate dosage using the most suitable route of administration compatible with the specific characteristics of both BTcP and the patient. It is essential that the patient be kept fully informed as to the specific pathogenetic mechanisms and clinical features of BTcP, as well as the pharmacological and safety profiles of the treatment options.

From a research perspective, it is vital to find a universally accepted nosological definition of BTcP, and to continually update evidence-based guidelines to keep pace with the rapid evolution in available treatment options, and to counter misunderstandings caused by educational, cultural, organisational and therapeutic gaps in the way BTcP is managed. Better information and training regarding this issue, as well as the establishment of dedicated organisational structures (multidisciplinary teams, centres of

excellence, etc.) will break down cultural barriers regarding BTcP and the use of opioids, and ensure that patients are given optimal treatment for this debilitating type of pain.

Compliance with Ethic Standards

Conflict of interest Guido Fanelli, Carlo Peruselli, Sebastiano Adamo, Geraldo Alongi, Francesco Amato, Leonardo Consoletti, Simeone Liguori, Antonio Maione, Sergio Mameli, Sandro Marulli, Vincenzo Minotti, Danilo Miotti, Luigi Montanari, Giovanni Moruzzi, Salvatore Palermo, Massimo Parolini, Paolo Poli and Walter Tirelli declared no conflict of interest.
Renato Vellucci declares no financial, personal and commercial disclosures. He had academic relationships with pharmaceutical industries (Grunenthal, Molteni, Norgine and italfarmaco) for intellectual scientific activities, participation to scientific boards, invitations to Meetings as speaker.

Funding All authors declare no funding was received in the preparation of this manuscript.

References

1. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain. 1990;41:273–81.
2. Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. Cancer. 2002;94:832–9.
3. Davies AN, Dickman A, Reid C, et al. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain. 2009;13:331–8.
4. Zeppetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. J Pain Symptom Manage. 2000;20:87–92.
5. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012;13:e58–68.
6. Zeppetella G, Davies A, Eijgelshoven I, Jansen JP. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. J Pain Symptom Manage. 2014;47(4):772–785.e5.
7. Smith HS. Considerations in selecting rapid-onset opioids for the management of breakthrough pain. J Pain Res. 2013;6:189–200.
8. Caraceni A, Martini C, Zecca E, et al. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. Palliat Med. 2004;18:177–83.
9. Deandrea S, Corli O, Consonni D, et al. Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. J Pain Symptom Manage. 2014;47:57–76.
10. Greco MT, Corli O, Montanari M, et al. Epidemiology and pattern of care of breakthrough cancer pain in a longitudinal sample of cancer patients: results from the Cancer Pain Outcome Research Study Group. Clin J Pain. 2011;27:9–18.
11. Mercadante S, Amadori D, Apolone G, et al. Raccomandazioni per la gestione del Breakthrough cancer Pain (BTcP). Riv Ital Cure Palliat. 2010;10:17–23.
12. Gatti A, Mediati RD, Reale C, et al. Breakthrough pain in patients referred to pain clinics: the Italian pain network retrospective study. Adv Ther. 2012;29:464–72.
13. Margarit C, Julia J, Lopez R, et al. Breakthrough cancer pain—still a challenge. J Pain Res. 2012;5:559–66.
14. Knudsen AK, Brunelli C, Kaasa S, et al. Which variables are associated with pain intensity and treatment response in advanced cancer patients? Implications for a future classification system for cancer pain. Eur J Pain. 2011;15:320–7.
15. Coluzzi PH. Cancer pain management: newer perspectives on opioids and episodic pain. Am J Hosp Palliat Care. 1998;15:13–22.
16. Payne R. Recognition and diagnosis of breakthrough pain. Pain Med. 2007;8(Suppl 1):S3–7.
17. Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. Pain. 2003;101:55–64.
18. Haugen DF, Hjermstad MJ, Hagen N, et al. Assessment and classification of cancer breakthrough pain: a systematic literature review. Pain. 2010;149:476–82.
19. Simmonds MA. Management of breakthrough pain due to cancer. Oncology (Williston Park). 1999;13:1103–8 **(discussion 1110, 1113–1114)**.
20. Hagen NA, Stiles C, Nekolaichuk C, et al. The Alberta Breakthrough Pain Assessment Tool for cancer patients: a validation study using a delphi process and patient think-aloud interviews. J Pain Symptom Manage. 2008;35:136–52.
21. Webber K, Davies AN, Zeppetella G, Cowie MR. Development and validation of the breakthrough pain assessment tool (BAT) in cancer patients. J Pain Symptom Manage. 2014;48(4):619–31.
22. Bennett D, Burton AW, Fishman S, et al. Consensus Panel recommendations for the assessment and management of breakthrough pain. Part I assessment. Pharm Ther. 2005;30:296–301.
23. Jacobsen R, Moldrup C, Christrup L, Sjogren P. Patient-related barriers to cancer pain management: a systematic exploratory review. Scand J Caring Sci. 2009;23:190–208.
24. Schumacher KL, West C, Dodd M, et al. Pain management autobiographies and reluctance to use opioids for cancer pain management. Cancer Nurs. 2002;25:125–33.
25. Schumacher KL, Koresawa S, West C, et al. Putting cancer pain management regimens into practice at home. J Pain Symptom Manage. 2002;23:369–82.
26. American Pain F. Breakthrough cancer pain: mending the break in the continuum of care. J Pain Palliat Care Pharmacother. 2011;25:252–64.
27. Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. J Pain. 2002;3:38–44.
28. Fortner BV, Demarco G, Irving G, et al. Description and predictors of direct and indirect costs of pain reported by cancer patients. J Pain Symptom Manage. 2003;25:9–18.
29. Bernabei R, Gambassi G, Lapane K, et al. Management of pain in elderly patients with cancer. SAGE Study Group. Systematic assessment of geriatric drug use via epidemiology. JAMA. 1998;279:1877–82.
30. Laverty D, Davies A. Assessment. In: Davies A, editor. Cancer-related breakthrough pain. Oxford: Oxford University Press; 2006. p. 23–30.
31. Oechsle K, Goerth K, Bokemeyer C, Mehnert A. Symptom burden in palliative care patients: perspectives of patients, their

family caregivers, and their attending physicians. Support Care Cancer. 2013;21:1955–62.
32. Laugsand EA, Sprangers MA, Bjordal K, et al. Health care providers underestimate symptom intensities of cancer patients: a multicenter European study. Health Qual Life Outcomes. 2010;8:104.
33. Parlow JL, Milne B, Tod DA, et al. Self-administered nitrous oxide for the management of incident pain in terminally ill patients: a blinded case series. Palliat Med. 2005;19:3–8.
34. Bell BC, Butler EB. Management of predictable pain using fentanyl pectin nasal spray in patients undergoing radiotherapy. J Pain Res. 2013;6:843–8.
35. Webber K, Davies AN, Cowie MR. Breakthrough pain: a qualitative study involving patients with advanced cancer. Support Care Cancer. 2011;19:2041–6.
36. Rhiner MI, von Gunten CF. Cancer breakthrough pain in the presence of cancer-related chronic pain: fact versus perceptions of health-care providers and patients. J Support Oncol. 2010;8:232–8.
37. Zeppetella G. Evidence-based treatment of cancer-related breakthrough pain with opioids. J Natl Compr Canc Netw. 2013;11(Suppl 1):S37–43.
38. Vissers D, Stam W, Nolte T, et al. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. Curr Med Res Opin. 2010;26:1037–45.
39. Meriggi F, Zaniboni A. Fentanyl for breakthrough cancer pain: where are we? Rev Recent Clin Trials. 2013;8:42–7.
40. Novotna S, Valentova K, Fricova J, Richterova E, Harabisova S, Bullier F. Trinquet F; ETHYFYL Study Group. A randomized, placebo-controlled study of a new sublingual formulation of fentanyl citrate (fentanyl ethypharm) for breakthrough pain in opioid-treated patients with cancer. Clin Ther. 2014;36:357–67.
41. Kress HG, Oronska A, Kaczmarek Z, et al. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. Clin Ther. 2009;31:1177–91.
42. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain. 2006;22:805–11.
43. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. J Support Oncol. 2007;5:327–34.
44. Mercadante S, Radbruch L, Davies A, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial. Curr Med Res Opin. 2009;25:2805–15.
45. Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients. Cochrane Database Syst Rev. 2013;10:CD004311.
46. Zeppetella G. Opioids for the management of breakthrough cancer pain in adults: a systematic review undertaken as part of an EPCRC opioid guidelines project. Palliat Med. 2011;25:516–24.
47. Mercadante S, Villari P, Ferrera P, et al. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. Br J Cancer. 2007;96:1828–33.
48. Hagen NA, Fisher K, Victorino C, Farrar JT. A titration strategy is needed to manage breakthrough cancer pain effectively: observations from data pooled from three clinical trials. J Palliat Med. 2007;10:47–55.
49. Coluzzi PH, Schwartzberg L, Conroy JD, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain. 2001;91:123–30.
50. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain. 1999;81:129–34.
51. Zeppetella G. Impact and management of breakthrough pain in cancer. Curr Opin Support Palliat Care. 2009;3:1–6.
52. Hans GH. Treatment of breakthrough cancer pain: to titrate or to proportionate? Curr Med Res Opin. 2013;29:1523–6.
53. Smith H. A comprehensive review of rapid-onset opioids for breakthrough pain. CNS Drugs. 2012;26:09–535.
54. Sima L, Fang WX, Wu XM, Li F. Efficacy of oxycodone/paracetamol for patients with bone-cancer pain: a multicenter, randomized, double-blinded, placebo-controlled trial. J Clin Pharm Ther. 2012;37:27–31.
55. Breuer B, Fleishman SB, Cruciani RA, Portenoy RK. Medical oncologists' attitudes and practice in cancer pain management: a national survey. J Clin Oncol. 2011;29:4769–75.
56. Dickman A. Integrated strategies for the successful management of breakthrough cancer pain. Curr Opin Support Palliat Care. 2011;5:8–14.
57. Portenoy RK, Raffaeli W, Torres LM, et al. Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients. J Opioid Manage. 2010;6:319–28.
58. Rauck R, North J, Gever LN, et al. Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. Ann Oncol. 2010;21:1308–14.